138. (Amended) **[A]** The method according to **[either]** claim 132 **[or 135]**, wherein said trait is cancer, prostate cancer, an early onset of prostate cancer, a beneficial response to or side effects related to treatment or a vaccination against prostate cancer, a susceptibility to prostate cancer, the level of aggressiveness of prostate cancer tumors, a modified or forthcoming expression of the PCTA-1 gene, a modified or forthcoming production of the PCTA-1 protein**[,]** or the production of a modified PCTA-1 protein.

140. (Amended) **[A]** The method according to**[either]** claim 132 **[or 135]**, wherein said control population is a trait negative population.

141. (Amended) **[A]** The method according to**[either]** claim 132 **[or 135]**, wherein said control population is a random population.

151. (Amended) **[A]** The method according to **[any one of]** claim**[s]** 121**[, 131, 132, 133, 135, and 150]**, wherein said PCTA-1-related biallelic marker is selected from the group consisting of **[A1 to A125]** biallelic markers of SEQ ID No:1 located at positions 278, 402, 472, 2955, 12167, 12536, 17593, 17606, 22079, 28964, 29003, 31077, 31766, 34791, 45751, 49847, 49855, 49886, 49900, 49906, 49921, 49939, 50256, 54955, 64239, 65436, 65496, 66967, 66987, 67092, 67129, 67229, 67433, 67723, 67834, 67955, 68213, 68263, 68375, 68477, 68525, 68594, 68610, 70566, 70728, 80038, 80118, 80170, 80183, 80435, 82090, 82165, 82169, 82218, 82234, 82268, 82393, 83587, 83643, 83644, 83808, 83881, 83884, 83909, 83937, 83947, 83982, 83988, 84047, 84092, 84145, 85202, 86259, 86323, 87713, 87735, 87787, 87806, 87860, 87902, 87980, 88012, 88215, 88283, 88297, 88442, 88471, 88480, 89394, 89464, 89471, 89658, 92760, 93023, 93055, 93247, 93319, 93323, 93388, 93393, 93418, 93515, 93726, 93903, 94170, 94218, 94269, 94290, 94422, 94432, 94720, 94989, 95261, 95340, 95497, 95770, 95819, 96145, 96181, 96350, 96951, 97144, 97276, 102267, 105937 and **[the]** complements thereof.

152. (Amended) **[A]** The method according to claim 150, wherein said PCTA-1-related biallelic marker is selected from the group consisting **[following list]** of biallelic markers of SEQ ID No:1 located at positions 402, 67092, 68525, 82234, 82393 **[: A2, A30, A41, A55 and A57,]**

and [the] complements thereof.

Please add the following claims.

163. (New) The method according to claim 135, wherein said trait is cancer, prostate cancer, an early onset of prostate cancer, a beneficial response to or side effects related to treatment or a vaccination against prostate cancer, a susceptibility to prostate cancer, the level of aggressiveness of prostate cancer tumors, a modified or forthcoming expression of the PCTA-1 gene, a modified or forthcoming production of the PCTA-1 protein or the production of a modified PCTA-1 protein.

164. (New) The method according to claim 163, wherein said trait is prostate cancer.

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165. (New) The method according to claim 135, wherein said control population is a trait negative population.

166. (New) The method according to claim 135, wherein said control population is a random population.

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167. (New) The method according to claim 131, wherein said PCTA-1-related biallelic marker is selected from the group consisting of biallelic markers of SEQ ID No:1 located at positions 278, 402, 472, 2955, 12167, 12536, 17593, 17606, 22079, 28964, 29003, 31077, 31766, 34791, 45751, 49847, 49855, 49886, 49900, 49906, 49921, 49939, 50256, 54955, 64239, 65436, 65496, 66967, 66987, 67092, 67129, 67229, 67433, 67723, 67834, 67955, 68213, 68263, 68375, 68477, 68525, 68594, 68610, 70566, 70728, 80038, 80118, 80170, 80183, 80435, 82090, 82165, 82169, 82218, 82234, 82268, 82393, 83587, 83643, 83644, 83808, 83881, 83884, 83909, 83937, 83947, 83982, 83988, 84047, 84092, 84145, 85202, 86259, 86323, 87713, 87735, 87787, 87806, 87860, 87902, 87980, 88012, 88215, 88283, 88297, 88442, 88471, 88480, 89394, 89464, 89471, 89658, 92760, 93023, 93055, 93247, 93319, 93323, 93388, 93393, 93418, 93515, 93726, 93903, 94170, 94218, 94269, 94290, 94422, 94432, 94720, 94989, 95261, 95340, 95497, 95770, 95819, 96145, 96181, 96350, 96951, 97144, 97276, 102267, 105937 and complements thereof.

168. (New) The method according to claim 132, , wherein said PCTA-1-related biallelic marker is selected from the group consisting of biallelic markers of SEQ ID No:1 located at positions 278, 402, 472, 2955, 12167, 12536, 17593, 17606, 22079, 28964, 29003, 31077, 31766, 34791, 45751, 49847, 49855, 49886, 49900, 49906, 49921, 49939, 50256, 54955, 64239, 65436, 65496, 66967, 66987, 67092, 67129, 67229, 67433, 67723, 67834, 67955, 68213, 68263, 68375, 68477, 68525, 68594, 68610, 70566, 70728, 80038, 80118, 80170, 80183, 80435, 82090, 82165, 82169, 82218, 82234, 82268, 82393, 83587, 83643, 83644, 83808, 83881, 83884, 83909, 83937, 83947, 83982, 83988, 84047, 84092, 84145, 85202, 86259, 86323, 87713, 87735, 87787, 87806, 87860, 87902, 87980, 88012, 88215, 88283, 88297, 88442, 88471, 88480, 89394, 89464, 89471, 89658, 92760, 93023, 93055, 93247, 93319, 93323, 93388, 93393, 93418, 93515, 93726, 93903, 94170, 94218, 94269, 94290, 94422, 94432, 94720, 94989, 95261, 95340, 95497, 95770, 95819, 96145, 96181, 96350, 96951, 97144, 97276, 102267, 105937 and complements thereof.

169. (New) The method according to claim 133, wherein said PCTA-1-related biallelic marker is selected from the group consisting of biallelic markers of SEQ ID No:1 located at positions 278, 402, 472, 2955, 12167, 12536, 17593, 17606, 22079, 28964, 29003, 31077, 31766, 34791, 45751, 49847, 49855, 49886, 49900, 49906, 49921, 49939, 50256, 54955, 64239, 65436, 65496, 66967, 66987, 67092, 67129, 67229, 67433, 67723, 67834, 67955, 68213, 68263, 68375, 68477, 68525, 68594, 68610, 70566, 70728, 80038, 80118, 80170, 80183, 80435, 82090, 82165, 82169, 82218, 82234, 82268, 82393, 83587, 83643, 83644, 83808, 83881, 83884, 83909, 83937, 83947, 83982, 83988, 84047, 84092, 84145, 85202, 86259, 86323, 87713, 87735, 87787, 87806, 87860, 87902, 87980, 88012, 88215, 88283, 88297, 88442, 88471, 88480, 89394, 89464, 89471, 89658, 92760, 93023, 93055, 93247, 93319, 93323, 93388, 93393, 93418, 93515, 93726, 93903, 94170, 94218, 94269, 94290, 94422, 94432, 94720, 94989, 95261, 95340, 95497, 95770, 95819, 96145, 96181, 96350, 96951, 97144, 97276, 102267, 105937, and complements thereof.

170. (New) The method according to claim 135, wherein said PCTA-1-related biallelic marker is selected from the group consisting of biallelic markers of SEQ ID No:1 located at positions 278, 402, 472, 2955, 12167, 12536, 17593, 17606, 22079, 28964, 29003, 31077,

31766, 34791, 45751, 49847, 49855, 49886, 49900, 49906, 49921, 49939, 50256, 54955, 64239, 65436, 65496, 66967, 66987, 67092, 67129, 67229, 67433, 67723, 67834, 67955, 68213, 68263, 68375, 68477, 68525, 68594, 68610, 70566, 70728, 80038, 80118, 80170, 80183, 80435, 82090, 82165, 82169, 82218, 82234, 82268, 82393, 83587, 83643, 83644, 83808, 83881, 83884, 83909, 83937, 83947, 83982, 83988, 84047, 84092, 84145, 85202, 86259, 86323, 87713, 87735, 87787, 87806, 87860, 87902, 87980, 88012, 88215, 88283, 88297, 88442, 88471, 88480, 89394, 89464, 89471, 89658, 92760, 93023, 93055, 93247, 93319, 93323, 93388, 93393, 93418, 93515, 93726, 93903, 94170, 94218, 94269, 94290, 94422, 94432, 94720, 94989, 95261, 95340, 95497, 95770, 95819, 96145, 96181, 96350, 96951, 97144, 97276, 102267, 105937 and complements thereof.

171. (New) The method according to claim 150, wherein said PCTA-1-related biallelic marker is selected from the group consisting of biallelic markers of SEQ ID No:1 located at positions 278, 402, 472, 2955, 12167, 12536, 17593, 17606, 22079, 28964, 29003, 31077, 31766, 34791, 45751, 49847, 49855, 49886, 49900, 49906, 49921, 49939, 50256, 54955, 64239, 65436, 65496, 66967, 66987, 67092, 67129, 67229, 67433, 67723, 67834, 67955, 68213, 68263, 68375, 68477, 68525, 68594, 68610, 70566, 70728, 80038, 80118, 80170, 80183, 80435, 82090, 82165, 82169, 82218, 82234, 82268, 82393, 83587, 83643, 83644, 83808, 83881, 83884, 83909, 83937, 83947, 83982, 83988, 84047, 84092, 84145, 85202, 86259, 86323, 87713, 87735, 87787, 87806, 87860, 87902, 87980, 88012, 88215, 88283, 88297, 88442, 88471, 88480, 89394, 89464, 89471, 89658, 92760, 93023, 93055, 93247, 93319, 93323, 93388, 93393, 93418, 93515, 93726, 93903, 94170, 94218, 94269, 94290, 94422, 94432, 94720, 94989, 95261, 95340, 95497, 95770, 95819, 96145, 96181, 96350, 96951, 97144, 97276, 102267, 105937 and complements thereof.

REMARKS

Applicants have elected to prosecute Claims 121-141 and 150-152. Claims 1-120, 142-149, and 153-162 were withdrawn from consideration. As a result of the present amendment, new Claims 163-171 have been added. Thus, Claims 121-141, 150-152, and 163-171 are currently pending in the application.

Claim Objections

The Examiner has objected to Claim 131 because the claim concludes with two periods. Applicants have amended Claim 131 to remove the extraneous period. This amendment was not made for a reason substantially related to patentability but rather to remove a typographical error.

Claim Rejections under 35 U.S.C. §112

The Examiner has rejected Claims 151 and 152 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the individual matter which Applicants regard as the invention. The Examiner states that Claims 151 and 152 recite biallelic markers selected from the group consisting of "A1 to A125" or "A2, A30, A41, A55 and A57" but that "[i]t is not clearly recited what these numbers represent" and that "[n]o recitation is made as to what is being referred." (Office Action, page 2).

Applicants respectfully submit that these numbers refer to PCTA-1 biallelic markers, which are clearly defined in the specification. (*See* the section entitled "PCTA-1 related biallelic markers" and page 59, line 27 to page 60, line 8). In addition, the position of each of the 125 biallelic markers named A1 to A125 is provided in Table 2. (*See* pages 178 to 182). A fundamental principle is that applicants are their own lexicographers. (*See* M.P.E.P. §2173.01). Because the specification clearly defines the biallelic markers "A1 to A125" or "A2, A30, A41, A55 and A57", Applicants believe that Examiner's rejection under 35 U.S.C. §112 is misplaced.

Nevertheless, to expedite allowance of this application, Applicants have amended Claims 151 and 152 to recite the positions of the biallelic markers "A1 to A125" or "A2, A30, A41, A55 and A57" with reference to SEQ ID No:1. As stated above, support for this amendment can be found in Table 2 (*See* pages 178 to 182). By this amendment, Applicants have imported definitions set forth in the specification into the claims and have removed the terms, which were used to represent these definitions, so as to preempt further argument and expedite allowance of

this application. Accordingly, this amendment was not made for a reason substantially related to patentability. Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

Claim Rejections under 35 U.S.C. §103

The Examiner has rejected Claims 121-126 and 150 under 35 U.S.C. §103(a), as allegedly being unpatentable over Barany, (US Patent 6,027,889) in view of Su et al., (Proc. Natl. Acad. Sci. USA, 93:7252-7257, (1996)). The Examiner argues that Barany "discloses a method of detection of nucleic acid sequences, the method being used in the detection of human cancers such as prostate cancer and involving oncogenes, tumor suppressor genes or genes involved in DNA amplification with polymerase chain reactions, replication, recombination, or repair." (*See* Office Action, page 3). The Examiner correctly notes that Barany does not explicitly teach the identification of the nucleic acid sequences at a PCTA-1-related biallelic marker.

The Examiner attempts to fill this void with the teaching provided by Su et al. The Examiner states that Su et al., "teaches the PCTA-1 gene and its association with human prostate cancer." (*See* Office Action, page 3). The Examiner further states that "Su suggests direct applications for prostate cancer diagnosis and staging. The Examiner then concludes that Claims 121-126 and 150 are obvious because one of skill in the art at the time the invention was made would be motivated to modify the teachings of Barany by identifying the nucleic acid sequences at sites known to be associated with prostate cancer, since Su suggests that the PCTA-1 gene is associated with human prostate cancer.

Applicants respectfully submit that the combination of Barany and Su et al. do not teach, suggest or motivate one of skill in the art to realize all of the limitations of the claims with a reasonable expectation of success. Further, Applicants respectfully submit that the combination of Barany and Su et al., is inappropriate because neither Barany or Su et al. contain the requisite suggestion or motivation to combine.

In particular, the cited references provide no demonstration or suggestion that the PCTA-1 gene is a causative agent of prostate cancer, no demonstration or suggestion that PCTA-1 related biallelic markers exist, no demonstration or suggestion that PCTA-1 related biallelic markers are associated with a trait, and no demonstration or suggestion of the locations or identities of the specific biallelic PCTA-1 related biallelic markers identified by the Applicants.

As recognized by the Examiner, Baranay does not teach or suggest the identification of nucleic acid sequences at a PCTA-1-related biallelic marker. Similarly, Su et al. does not teach or suggest the identification of nucleic acids at a PCTA-1-related biallelic marker. Thus, these references in combination cannot teach all of the limitations of the claims. In particular, the combination of Baranay and Su et al. cannot be said to make obvious the specific biallelic markers claimed because the existence, position and identity of these markers on the PCTA-1 genomic sequence had not been conceived until Applicants invention.

In fact, Baranay is merely a general reference for detecting nucleic acid sequence differences that only provides an invitation to try to find biallelic markers on several different genes associated with several different types of cancer. Baranay never mentions the PCTA-1 gene and mentions prostate cancer only in passing. Baranay states:

> Cancers which can be detected by the process of the present invention generally involve oncogenes, tumor suppressor genes, or genes involved in DNA amplification, replication, recombination, or repair. Examples of these include: BRCA1 gene, p53 gene, APC gene, Her2/Neu amplification, Bcr/Ab1, K-ras gene, and human papillomavirus Types 16 and 18. Various aspects of the present invention can be used to identify amplifications, large deletions as well as point mutations and small deletions/insertions of the above genes in the following common human cancers: leukemia, colon cancer, breast cancer, lung cancer, prostate cancer, brain tumors, central nervous system tumors, bladder tumors, melanomas, liver cancer, osteosarcoma and other bone cancers, testicular and ovarian carcinomas, head and neck tumors, and cervical neoplasms. (Baranay, Column 35, lines 12-26).

Baranay's laundry list of possible applications does not amount to a suggestion or motivation to determine biallelic markers on the PCTA-1 genomic sequence that are associated with prostate cancer. Baranay's failure to identify the PCTA-1 gene as the source for biallelic

markers associated with prostate cancer leaves the skilled artisan with nothing more than general techniques for determining biallelic markers and the recognition that many cancers, including prostate cancer, generally involve oncogenes, tumor suppressor genes, or genes involved in DNA amplification, replication, recombination, or repair. Surely, this broad invitation to conduct research does not suggest or motivate the combination with Su et al.

Su et al., describes the observation that human prostate cancer cell lines express the PCTA-1 protein. However, the observation that a protein is expressed in cancerous cells does not indicate whether the protein is the causative agent of the cancer or merely a response to cancer induced by another protein. Thus, prior to Applicants' invention, there was no demonstration that PCTA-1 is a causative agent of prostate cancer, nor there was a demonstration that PCTA-1 related biallelic markers exist at all. In addition, prior to Applicants' invention, there was no demonstration that PCTA-1 related biallelic markers can be associated with a trait or that the specific PCTA-1 related biallelic markers identified by the Applicants even existed.

Su's uncertainty regarding whether PCTA-1 is a causative agent of prostate cancer or merely a protein produced in response to prostate cancer is reflected in the statement "[i]t will also be important to ascertain if inhibition of PCTA-1 expression, using antisense oligonucleotides, antisense expression vectors, or ribozyme approaches, alters the tumorigenic or metastatic properties of human prostate cancers." (Su et al., page 7257). Because Su et al. only monitored the expression of PCTA-1, they could not be certain whether PCTA-1 is involved in tumorigenesis or metastasis of prostate cancer, is only expressed as the result of prostate cells becoming cancerous, or is expressed due to a defective gene upstream in the tumorigenesis pathway.

Applicants note that there have been several instances where expression of a protein was correlated with cancer but the protein was produced in response to cancer rather than being the causative agent of the cancer. In such instances, biallelic markers in the genes encoding the protein will not exhibit an association with cancer. In contrast, Applicants have detected an

association between PCTA-1 related biallelic markers and prostate cancer, thereby demonstrating both the involvement of PCTA-1 as a causative agent of prostate cancer and the fact that PCTA-1 related biallelic markers may be used to detect an association with a trait.

In particular, Applicants note the following examples of proteins which are expressed in response to cancer rather than being causative agents. The p73 gene, for example, encodes a protein that is similar to p53. (*See* Kang et al., Clin. Res. Cancer (2000); 6: 1767-71; Exhibit A). An allotyping study using a p73 polymorphism in exon 2 showed that p73 was overexpressed in gastric carcinomas because of overexpression of a variant molecule. This study failed to show that a deletion or mutation of p73 was present in cancerous cells nor did it correlate p73 overexpression with either the mutational status of p53 or expression of p21Waf1, a p53-responsive gene. Further, the authors demonstrated that p73 expression was induced by serum starvation or cellular clump formation. Together, these results provide evidence that p73 is overexpressed because of monoallelic transcriptional induction of an active allele and/or the activation of a silent allele that may be triggered by physiological stresses accompanied by outgrowth of tumors such as hypoxia or nutrient deprivation rather than genetic alteration. (*Id.*).

Another example of a gene that is expressed or overexpressed by cancer cells in response to becoming cancerous is the cyclin D1/CCND1 oncogene. (Hosokawa and Arnold, Genes Chromosom. Cancer (1998); 22: 66-71; Exhibit B). This gene is overexpressed in 30-50% of breast cancers at a degree higher than accounted for by cyclin D1 gene amplification, as well as, in other cells of different cancerous origin in which neither translocation or gene amplification has been reported. Analysis of allele-specific expression of the cyclin/CCND1 oncogene in breast, sarcoma, and colon cancers that exhibit cyclin D1 overexpression and normal gene copy number, failed to demonstrate an association of a NciI polymorphic site within exon 4 of the gene with overexpression of a specific cyclin D1 allele. Thus, cyclin D1 overexpression is thought to result from a trans-acting influence on both cyclin D1 alleles rather than from a clonal somatic mutation in or near a single cyclin D1 gene. (*Id.*).

Still another example of a gene that is expressed or overexpressed by cancer cells in response to becoming cancerous is the hOGG1 gene. (Kondo et al., Clin. Cancer Res. (2000); 6: 1394-1400; Exhibit C). The hOGG1 gene encodes the 8-hydroxy-2'-deoxyguanosine (8-OHdG)-specific lyase, which is a protein that efficiently removes one of the most abundant oxidatively modified lesions in DNA, namely 8-OHdG. Colorectal carcinoma cells are exposed to an increased level of oxidative stress characterized by an increased 8-OHdG level. This increase has been correlated with a proportionate increase in the levels of 8-OHdG-specifc lyase activity and hOGG1 expression. Of the 3 observed hOGG1 polymorphisms, none were correlated with a different 8-OHdG-specifc lyase activity in normal versus cancerous cells and a hOGG1 mutation was not found in any of the 25 cases of colorectal carcinomas examined. (*Id.*).

Furthermore, even if a gene is the causative agent of cancer, one may not be able to identify biallelic markers in the gene which are associated with cancer. An example of a gene that is overexpressed in cancer cells and involved in tumorigenesis is the proliferating cell nuclear antigen (PCNA), which encodes a multifunctional protein that is involved in DNA replication and damage repair. (Ma et al., Int. J. Cancer (2000); 88: 938-42; Exhibit D). PCNA is expressed in fast growing cells and tumor cells. Yeast models had suggested an association of mutant forms of PCNA with genomic instability. In addition, overexpression of PCNA in mammalian cells negate growth arrest induced by serum starvation and cell contact, thus raising the possibility that PCNA was involved in disruption of growth control leading to malignant transformation (Fukami-Koyabashi and Mitsui, Jpn. J. Cancer Res. 1999; 90(3): 286-93). Out of the nine biallelic markers found on the PCNA genomic sequence, six intronic biallelic markers showed complete linkage disequilibrium, and none exhibited a statistically significant frequency difference compared to healthy controls in any of the cancer types tested (37 melanomas,118 breast cancers and 100 lung cancers).

The four examples provided above not only demonstrate that the field is highly unpredictable but underscore the point that Applicants discovery of biallelic markers on the PCTA-1 genomic sequence was unexpected. As set forth in the foregoing examples, knowledge of techniques to identify the presence of biallelic markers on a gene and the observation that

expression of a gene is elevated in cancer cells does not predict whether biallelic markers will be present or whether biallelic markers can be correlated with the cancer. Thus, the general teaching of Baranay combined with the observations of Su et al., cannot suggest the presence or absence of biallelic markers on the PCTA-1 gene or their correlation with prostate cancer.

For the foregoing reasons, the combination of Barany and Su et al. does not teach or suggest that PCTA-1 is the causative agent of prostate cancer, that PCTA-1 biallelic markers associated with a trait exist, or that the particular PCTA-1 related biallelic markers identified by the Applicants exist. In view of the foregoing, Applicants respectfully request that the Examiner withdraw the rejections of Claims 121-126 and 150 under 35 U.S.C §103 as being unpatentable over Baranay and Su et al..

The Examiner has also rejected claims 121-130 and 150 under 35 U.S.C. §103, as being unpatentable over Barany in view of Su et al., and in further view of Simons (US Patent 5,612,179) and Syvanen et al. (Am. J. Hum. Genet., 52:46-59 (1993)). As explained earlier, Barany merely discloses general methods of detection of nucleic acid differences and Su et al. does not teach or suggest that PCTA-1 is the causative agent of prostate cancer, that PCTA-1 biallelic markers associated with a trait exist, or that the particular PCTA-1 related biallelic markers identified by the Applicants exist.

Simons discloses a general method for detection of alleles and haplotypes through analysis of an amplified genomic DNA sequence characteristic of a given allele. Such an amplified DNA sequence is then analyzed to detect the presence of a genetic variation using different methods depending on the type of genetic variation and including hybridization assays, electrophoresis eventually coupled with endonuclease digestion, or sequencing. Syvanen et al. disclose a general method of identification of individuals through detection of biallelic markers using PCR and solid-phase minisequencing.

As explained above, the combination of the general methods for the detection of biallelic markers with the observation that expression of PCTA-1 is elevated in prostate cancer cells does

not render the claimed invention obvious. Since Barany, Simons, and Syvanen are merely general methods for detecting nucleic acid differences, their combination with Su et al. does not render the claimed invention obvious.

Furthermore, since the patentability of claims 127-130, which are dependent on Claim 121, does not hinge on different methods of determining the identity of a nucleotide, the teachings of Simons and Syvanen et al. in combination of Barany and Su et al. do not render obvious claims 127-130.

Accordingly, Applicants respectfully request that the rejections of Claims 121-130 and 150 under 35 U.S.C. §103 as being unpatentable over the combination of Baranay, Su et al., Simons and Syvanen et al. be withdrawn.

The Examiner has also rejected Claims 121-126, 131-141 and 150 under 35 U.S.C. §103, as being unpatentable over Barany in view of Su et al., and Erlich (US Patent 5,110,920). Erlich discloses general methods for HLA typing based on analysis of HLA DNA restriction fragment length polymorphisms (RFLPs). As discussed above, the combination of general methods of detecting nucleic acid differences with Su et al. does not render the claimed invention obvious. Accordingly, Claims 121-126, and 150 are not obvious over Barany, in view of Su et al., and in further view of Erlich.

In addition, since the patentability of claims 131-141 which depend on claim 121, does not hinge on methods of determination of i) the frequency of alleles or haplotypes, 2) association between a trait and an haplotype or an allele and iii), a relative risk of developing a given disorder, the teachings of Erlich are not additive to the combination of Barany and Su et al. Accordingly, Applicants respectfully request that the rejections of Claims Claims 121-126, 131-141 and 150 under 35 U.S.C. §103 as being unpatentable over the combination of Baranay, Su et al., and Erlich be withdrawn.